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# **The APEX Trial: Effects of Allopurinol on Exercise Capacity, Coronary and Peripheral Endothelial Function and Natriuretic Peptides in Patients with Cardiac Syndrome X**

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Trial registration with Clinicaltrials.gov. NCT00512057

Short Title: Allopurinol and Cardiac Syndrome X

Key words: Allopurinol, Cardiac Syndrome X, Exercise, Oxidative Stress.

Abstract Word count: 255; Total word count: 2324; Tables: 2; References: 16

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## **Abstract**

The role of endothelial dysfunction and oxidative stress in the pathogenesis of cardiac syndrome X has recently been recognised. Allopurinol has previously been shown to improve endothelial dysfunction, reduce oxidative stress burden and improve myocardial efficiency. In this 'proof of concept' study, we investigated the effect of allopurinol on exercise capacity, coronary and peripheral endothelial function, and serum B-type natriuretic peptide (BNP: a marker of cardiac function and myocardial ischaemia) in patients with cardiac syndrome X.

## **Methods and Results**

This study was a randomised, double-blind, placebo-control crossover trial. Nineteen patients (mean age  $59 \pm 10$  years, 11 women & 8 men) with cardiac syndrome X were randomised to a 6-week treatment with either allopurinol (600mg/day) or placebo. After 4 weeks of washout period, they were crossed over to the other arm. Outcomes measured at baseline and after treatment were maximum exercise time (ET) derived from Bruce protocol exercise treadmill test, serum BNP measurement, coronary flow reserve (CFR) as assessed by measuring response of flow velocity in the left anterior descending artery to adenosine and flow-mediated vasodilatation of the brachial artery (FMD). Allopurinol significantly reduced serum uric acid levels when compared with placebo ( $-48 \pm 24\%$  vs  $1.9 \pm 11\%$ ,  $p < 0.001$ ). There was no significant difference in maximum ET, CFR and FMD between allopurinol and placebo. However, there was a trend that allopurinol reduced serum BNP when compared to placebo [ $-8\%$  (interquartile range  $-22$  to  $65\%$ ) vs  $44\%$  (interquartile range  $-18$  to  $140\%$ );  $p = 0.07$ ].

## **Conclusion**

In patients with cardiac syndrome X, high dose allopurinol did not improve exercise capacity, coronary or peripheral endothelial function.

## Introduction

Patients with cardiac syndrome X (typical anginal-like chest pain and normal coronary arteriograms) represent a heterogeneous syndrome, which encompasses different pathogenic mechanisms{ ADDIN EN.CITE

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C.</author><author>Aldama, G.</author><author>Cosin-Sales, J.</author></authors></contributors><auth-address>Coronary Artery Disease Research Unit, Cardiological Sciences, St George's Hospital Medical School, London, UK. jkaski@sghms.ac.uk</auth-address><titles><title>Cardiac syndrome X. Diagnosis, pathogenesis and management</title><secondary-title>Am J Cardiovasc Drugs</secondary-title></titles><periodical><full-title>Am J Cardiovasc Drugs</full-title></periodical><pages>179-

94</pages><volume>4</volume><number>3</number><keywords><keyword>Disease Management</keyword><keyword>Humans</keyword><keyword>\*Microvascular Angina/diagnosis/etiology/therapy</keyword></keywords><dates><year>2004</year></dates><accession-num>15134470</accession-num><urls><related-

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<EndNote><Cite><Author>Yaghoubi</Author><Year>2011</Year><RecNum>4473</RecNum><DisplayText><style face="superscript">2</style></DisplayText><record><rec-number>4473</rec-number><foreign-keys><key app="EN" db-id="sde022erm0xppvetvfyv9pv4azzevtattee9"

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M. Arefi, S. H. Assadi, M. Department of Cardiology, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran. Comparison of angiographic with myocardial perfusion scintigraphy findings in cardiac syndrome X (CSX) Eur Rev Med Pharmacol Sci 1385-8 15 12 Adult/keyword>Calcinosis/diagnosis/etiology/keyword>Coronary Angiography/ methods/keyword>Coronary Stenosis/diagnosis/etiology/keyword>Female/keyword>Human s/keyword>Male/keyword>Microvascular Angina/ diagnosis/pathology/keyword>Middle Aged/keyword>Myocardial Perfusion Imaging/ methods/keyword>/keywords><dates><year>2011</year><pub-dates><date>Dec</date></pub-dates></dates><isbn>1128-3602 (Print)&#xD;1128-3602 (Linking)</isbn><accession-num>22288299</accession-num><urls></urls></record></Cite></EndNote>}. Microvascular abnormalities, caused by coronary endothelial dysfunction, maybe responsible for myocardial ischemia in patients with cardiac syndrome X{ ADDIN EN.CITE <EndNote><Cite><Author>Hurst</Author><Year>2006</Year><RecNum>4474</RecNum><DisplayText><style face="superscript">3</style></DisplayText><record><rec-number>4474</rec-number><foreign-keys><key app="EN" db-id="sde022erm0xppvvetfyv9pv4azzevtattee9" timestamp="1491832875">4474</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Hurst, T.</author><author>Olson, T. H.</author><author>Olson, L. E.</author><author>Appleton, C. P.</author></authors></contributors><auth-address>Division of Cardiovascular Diseases, Mayo Clinic, Scottsdale, Arizona 85259, USA.</auth-address><titles><title>Cardiac syndrome X and endothelial dysfunction: new concepts in prognosis and treatment</title><secondary-title>Am J

Med</secondary-title></titles><periodical><full-title>Am J Med</full-title></periodical><pages>560-6</pages><volume>119</volume><number>7</number><keywords><keyword>Angiotensin-Converting Enzyme Inhibitors/therapeutic use</keyword><keyword>Endothelium, Vascular/physiopathology</keyword><keyword>Estrogens/deficiency/physiology</keyword><keyword>Humans</keyword><keyword>Hydroxymethylglutaryl-CoA Reductase Inhibitors/therapeutic use</keyword><keyword>Inflammation</keyword><keyword>Ischemia</keyword><keyword>Life Style</keyword><keyword>Microcirculation/pathology</keyword><keyword>Microvascular Angina/ drug therapy/ physiopathology</keyword><keyword>Pain Threshold</keyword><keyword>Prognosis</keyword><keyword>Risk Assessment</keyword></keywords><dates><year>2006</year><pub-dates><date>Jul</date></pub-dates></dates><isbn>1555-7162 (Electronic)&#xD;0002-9343 (Linking)</isbn><accession-num>16828624</accession-num><urls></urls></record></Cite></EndNote>}. Oxidative stress with increased production of reactive oxygen species may be one of the main mechanisms contributing to this microvascular endothelial dysfunction{ ADDIN EN.CITE <EndNote><Cite><Author>Cai</Author><Year>2000</Year><RecNum>172</RecNum><DisplayText><style face="superscript">4</style></DisplayText><record><rec-number>172</rec-number><foreign-keys><key app="EN" db-id="sde022erm0xppvvetfyv9pv4azzevtattee9" timestamp="0">172</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Cai, H.</author><author>Harrison, D. G.</author></authors></contributors><auth-address>Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA.</auth-address><titles><title>Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress</title><secondary-title>Circ Res</secondary-title></titles><periodical><full-title>Circ Res</full-title></periodical><pages>840-4</pages><volume>87</volume><number>10</number><keywords><keyword>Animal

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superoxide production has been shown to predict future cardiovascular events in this  
patient group{ ADDIN EN.CITE { ADDIN EN.CITE.DATA }} that might suggest an  
important pathophysiological role of oxidative stress. It has been proposed that the  
improvement in endothelial function observed with combined treatment with a statin and  
angiotensin-converting-enzyme (ACE) inhibitor in patients with cardiac syndrome X may  
be related to a reduction in oxidative stress{ ADDIN EN.CITE { ADDIN EN.CITE.DATA  
}}. However, to the best of knowledge, there have been no studies that have studied the  
direct effects of reducing oxidative stress in patients with cardiac syndrome X.

We have previously shown that high-dose allopurinol (600mg/day) improved  
endothelial function, as assessed by forearm venous occlusion plethysmograph in  
patients with chronic heart failure by its ability to reduce oxidative stress, independently  
of any effect on urate levels{ ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. Additionally,  
this high dose allopurinol markedly reduced vascular oxidative stress, as assessed by  
Vitamin C and acetylcholine co-infusion studies. These observations would suggest that  
allopurinol could be used to reduce oxidative stress in cardiac syndrome X. In this study,  
we hypothesized that allopurinol offers dual benefits of improving vascular function and  
reducing myocardial ischemia in patients with cardiac syndrome X. Thus, the objective



of this study was to investigate the effects of allopurinol on coronary and peripheral endothelial function, serum B-type natriuretic peptides (BNP- a marker of cardiac function and myocardial ischemia) and maximum exercise time on treadmill testing in patients with cardiac syndrome X.

## **Methods**

### **Study design**

This was a double-blind, crossover trial comparing the effects of allopurinol and placebo on exercise capacity, coronary and peripheral endothelial function and serum BNP levels in patients with this syndrome. Patients with cardiac syndrome X were randomised to a 6-week treatment with either allopurinol (600mg/day) or placebo. After 4 weeks of washout period, they were crossed over to the other arm.

### **Study patients**

After approval by the Scottish Research Ethics Committee (REC Ref: 07/S1401/103), eligible patients provided written informed consent to participate. We recruited patients with cardiac syndrome X that had smooth unobstructed epicardial arteries shown on coronary angiography at Ninewells Hospital, Dundee.

### ***Presence of symptoms and evidence of ischemia***

All had on-going typical anginal-type chest pain and at least one objective evidence of myocardial ischemia: Documented  $\geq 1$  mm of flat ST-segment depression on treadmill exercise testing and/or myocardial reversible perfusion abnormalities during adenosine stress as assessed by technetium-99m myocardial perfusion imaging.

All patients underwent pre-trial screening with blood tests and echocardiography. All had normal left and right ventricular structure and function with no evidence of significant valvular heart disease. All patients had given their written informed consent to participate in the study.

### **Study Protocol**

Following consent, participants continued on their usual anti-anginal medications that remained unchanged during the study period. A Flow Chart of this study is shown in Figure 1. In order to allow participants to be familiarised with exercise testing, all

underwent treadmill test 1 to 2 weeks prior starting study medication. Thereafter, they underwent a baseline exercise stress test and venesection for general hematological and biochemical analyses prior starting study medication (allopurinol or placebo). Patients were randomly assigned to treatment with either allopurinol or placebo 300 mg once daily for the first week, and then up-titrated to a maintenance dose of 300mg twice a day for further 5 weeks (total treatment period=6 weeks). At the end of this first treatment period, patients underwent a 4 weeks wash-out period after which they crossed over to the alternate treatment arm for another 6 weeks. Coronary vascular function, peripheral endothelial function, exercise testing and serum BNP level were carried out at baseline and repeated at the end of each treatment period by investigators who were blinded to treatment regimen. All studies were performed in the morning following an overnight fast and patients were not allowed to have caffeinated drinks or smoke for 12 hours before the tests.

## **Measurements of interest**

### ***Exercise Treadmill Test.***

The treadmill exercise test (an objective measure of myocardial ischaemia) was performed according to standard Bruce protocol. The exercise test was terminated when one or more of the following end points are reached: physical exhaustion, ST-segment depression { INCLUDEPICTURE "http://circ.ahajournals.org/math/ge.gif" \\* MERGEFORMATINET }0.3 mV, or severe arrhythmia. Measurement of interest included exercise duration.

### ***Assessment of Coronary Flow Reserve (CFR)***

Assessment of coronary vascular function were performed out by an experienced echocardiographer (TKL) who was blinded to the treatment regimen. Imaging of the left anterior descending (LAD) artery or perforating branches and measurement of coronary blood flow were carried out using a 7.0 MHz transducer (Acuson Sequoia 512, Siemens Medical Solutions, Berkshire, UK). Baseline spectral Doppler signals in the distal portion of the LAD coronary artery were recorded over five cardiac cycles at end-expiration. The endothelium-independent vasodilator capacity of the coronary microcirculation was assessed using spectral Doppler imaging during hyperemic condition following 2 min of

intravenous adenosine (140µg/kg/min) infusion. Mean diastolic velocities were measured at baseline and at peak hyperemic condition from the Doppler signal recordings. These measurements were averaged over three cardiac cycles. For adenosine infusion, CFR was defined as the ratio of hyperemic to basal mean diastolic velocities. The inter-observer and intra-observer variability for measurement of coronary Doppler velocity recordings in our laboratory were 4.9% and 4.0%, respectively. All patients had continuous heart rate and ECG monitoring. Blood pressure was recorded at baseline and during adenosine infusion, and at recovery.

### ***Assessment of Peripheral Endothelial Function***

#### ***Flow-mediated dilatation of brachial artery***

Flow-mediated vasodilatation (FMD) was assessed with ultrasound imaging of the brachial artery with a 15 MHz linear array ultrasound transducer connected to a Hewlett-Packard Sonos 5500 duplex ultrasound machine before and after a 5-minute occlusion of arterial flow in the upper extremity with inflation of a pneumatic cuff to suprasystolic pressures. Brachial artery diameter (long axis view) was measured at rest, and during peak hyperemia for 2 minutes. Brachial artery diameter measured at its maximum during the cardiac cycle with a computer-assisted edge detection system (NIH image analysis software). The percent change from baseline diameter to maximum diameter after hyperemia will be calculated as an index of flow-mediated vasodilatation in the brachial artery. Endothelium-independent vasodilatation was assessed with duplex ultrasound in the upper extremity before and 5 minutes after administration of 0.4 mg of sublingual nitroglycerin. We have an excellent intra-patient coefficient variation of only 2% in our vascular laboratory.

### **Statistical Methods**

Results from continuous data are shown as mean  $\pm$  1 standard deviation. Paired t test was used to compare the absolute differences for serum uric acids level, CFR, FMD and maximum exercise time before and after high dose of allopurinol/placebo treatment. The absolute percentage differences for serum BNP was obtained using Wilcoxon signed ranks test. A p value of < 0.05 (two-sided) was considered significant. Statistical

analysis was performed with Analyse-it software for Microsoft excel (Version 1.62, Analyse-it software Ltd, Leeds, United Kingdom). This study was powered for a 20% difference in exercise time, based on a previous study in patients with cardiac syndrome X { ADDIN EN.CITE { ADDIN EN.CITE.DATA }} with a mean exercise duration of 517sec and an SD of 114 sec. Power calculations demonstrated that a sample size of 19.2 will provide a power of 80% to detect a 20% difference in exercise time. This small 'proof of concept' study was not adequately powered to fully assess the effect of allopurinol on the discovery measures of CFR, FMD and BNP.

## Results

The clinical characteristics, past medical history and medications are shown in Table 1. Of the 19 (11 women & 8 men) cardiac syndrome X participants with mean age 59±10 years, 12 (63%) have a family history of coronary artery disease and 14 (74%) have a history of hypertension and hypercholesterolemia. None of them suffered from diabetes based on previous results of serum fasting glucose. Most participants were on anti-anginal therapy which includes beta-blockers, nitrate or calcium channel blockers. All patients completed the study.

Allopurinol treatment resulted in a significant reduction in serum uric acid levels when compared to placebo (-48±24% vs 1.9±11%,  $p<0.001$ ). However, there was no significant difference in maximum exercise time, CFR and FMD between allopurinol and placebo treatment arms (Table 2). There was a trend that allopurinol reduced serum BNP levels when compared to placebo [-8% (interquartile range -22 to 65%) vs 44% (interquartile range -18 to 140%);  $p=0.07$ ].

Noteworthy, there were no adverse effects of treatment reported.

## Discussion

Morbidity of patients with cardiac syndrome X is high and it is associated with continuing episodes of chest pain, hospital readmission. Importantly, a history of persistent chest pain in these patients has been shown to predict cardiovascular events{ ADDIN EN.CITE

<EndNote><Cite><Author>Johnson</Author><Year>2006</Year><RecNum>4478</Re

cNum><DisplayText><style face="superscript">9</style></DisplayText><record><rec-number>4478</rec-number><foreign-keys><key app="EN" db-id="sde022erm0xppvetfyv9pv4azzevtattee9" timestamp="1491833428">4478</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Johnson, BD</author><author>Shaw, LJ</author><author>Pepine, CJ</author><author>Reis, SE</author><author>Kelsey, SF</author><author>Sopko, G</author><author>Rogers, WJ</author><author>Mankad, S</author><author>Sharaf, BL</author><author>Bittner, V</author><author>Bailey Merz, CN</author></authors></contributors><auth-address>Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, PA, USA.</auth-address><titles><title>Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: results from the NIH-NHLBI-sponsored Women's Ischaemia Syndrome Evaluation (WISE) study</title><secondary-title>Eur Heart J</secondary-title></titles><periodical><full-title>Eur Heart J</full-title></periodical><pages>1408-15</pages><volume>27</volume><number>12</number><keywords><keyword>Aged</keyword><keyword>Cardiovascular Diseases</keyword><keyword>mortality</keyword><keyword>Chest Pain</keyword><keyword>diagnostic imaging</keyword><keyword>etiology</keyword><keyword>mortality</keyword><keyword>Coronary Angiography</keyword><keyword>Disease-Free Survival</keyword><keyword>Female</keyword><keyword>Follow-Up Studies</keyword><keyword>Humans</keyword><keyword>Middle Aged</keyword><keyword>Prognosis</keyword><keyword>Risk Factors</keyword></keywords><dates><year>2006</year><pub-dates><date>Jun</date></pub-dates></dates><isbn>0195-668X (Print)&#xD;0195-668X (Linking)</isbn><accession-num>16720691</accession-num><urls></urls></record></Cite></EndNote>}. Management of this syndrome represents a major challenge to the treating physician and understanding the mechanism underlying the condition is of vital importance for patient management. Conventional therapies with anti-anginal agents such as nitrates, calcium channel antagonists, classic  $\beta$ -adrenoceptor blockers and nicorandil have been tried with variable success{ ADDIN EN.CITE

<EndNote><Cite><Author>Lim</Author><Year>2009</Year><RecNum>4479</RecNum><DisplayText><style face="superscript">10</style></DisplayText><record><rec-number>4479</rec-number><foreign-keys><key app="EN" db-id="sde022erm0xppvetfyv9pv4azzevtattee9" timestamp="1491833599">4479</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Lim, T. K.</author><author>Choy, A. J.</author><author>Khan, F.</author><author>Belch, J. J.</author><author>Struthers, A. D.</author><author>Lang, C. C.</author></authors></contributors><auth-address>Division of Medicine and Therapeutics, University of Dundee, Dundee, UK.</auth-address><titles><title>Therapeutic development in cardiac syndrome X: a need to target the underlying pathophysiology</title><secondary-title>Cardiovasc Ther</secondary-title></titles><periodical><full-title>Cardiovasc Ther</full-title></periodical><pages>49-58</pages><volume>27</volume><number>1</number><keywords><keyword>Animal s</keyword><keyword>Antioxidants/ therapeutic use</keyword><keyword>Cardiovascular Agents/ therapeutic use</keyword><keyword>Cognitive Therapy</keyword><keyword>Endothelium, Vascular/ drug effects/physiopathology</keyword><keyword>Estrogen Replacement Therapy</keyword><keyword>Estrogens/deficiency</keyword><keyword>Exercise</keyword><keyword>Humans</keyword><keyword>Inflammation/metabolism/physiopathology/therapy</keyword><keyword>Insulin Resistance</keyword><keyword>Microcirculation/drug effects</keyword><keyword>Microvascular Angina/ drug therapy/metabolism/physiopathology</keyword><keyword>Myocardial Ischemia/metabolism/physiopathology/therapy</keyword><keyword>Oxidative Stress/ drug effects</keyword><keyword>Treatment Outcome</keyword></keywords><dates><year>2009</year><pub-dates><date>Spring</date></pub-dates></dates><isbn>1755-5914 (Print)&#xD;1755-5914 (Linking)</isbn><accession-num>19207480</accession-num><urls></urls></record></Cite></EndNote>}. However, this variable success might be related to a failure to target the underlying pathophysiology.

Allopurinol is not only a drug that has been used for treatment of gout; it has also been previously shown to reduce oxidative stress which is one of the important pathogenesis of cardiac syndrome X{ ADDIN EN.CITE

<EndNote><Cite><Author>Lim</Author><Year>2009</Year><RecNum>4479</RecNum><DisplayText><style face="superscript">10</style></DisplayText><record><rec-number>4479</rec-number><foreign-keys><key app="EN" db-

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K.</author><author>Choy, A. J.</author><author>Khan, F.</author><author>Belch, J. J.</author><author>Struthers, A. D.</author><author>Lang, C.

C.</author></authors></contributors><auth-address>Division of Medicine and Therapeutics, University of Dundee, Dundee, UK.</auth-

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58</pages><volume>27</volume><number>1</number><keywords><keyword>Animal s</keyword><keyword>Antioxidants/ therapeutic

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dates><date>Spring</date></pub-dates></dates><isbn>1755-5914 (Print)&#xD;1755-5914 (Linking)</isbn><accession-num>19207480</accession-num><urls></urls></record></Cite></EndNote>}. However in this current study, we showed that high dose allopurinol did not have any significant impact in exercise capacity on treadmill testing. Allopurinol also had no effect on endothelial function when assessed using echocardiographic Doppler derived CRF as well as by FMD of the brachial artery. These findings contrast with our previous study that showed that a similar high dose of allopurinol was able to improve exercise time in patients with chronic stable angina{ ADDIN EN.CITE

<EndNote><Cite><Author>Noman</Author><Year>2010</Year><RecNum>1056</RecNum><DisplayText><style face="superscript">11</style></DisplayText><record><rec-number>1056</rec-number><foreign-keys><key app="EN" db-id="sde022erm0xppvvetfyv9pv4azzevtattee9" timestamp="0">1056</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Noman, A.</author><author>Ang, D. S.</author><author>Ogston, S.</author><author>Lang, C. C.</author><author>Struthers, A. D.</author></authors></contributors><auth-address>Division of Medical Sciences, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK.</auth-address><titles><title>Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial</title><secondary-title>Lancet</secondary-title></titles><periodical><full-title>Lancet</full-title></periodical><pages>2161-7</pages><volume>375</volume><number>9732</number><edition>2010/06/15</edition><dates><year>2010</year><pub-dates><date>Jun 19</date></pub-dates></dates><isbn>1474-547X (Electronic)&#xD;0140-6736 (Linking)</isbn><accession-num>20542554</accession-num><urls></urls><custom2>2890860</custom2><electronic-resource-num>S0140-6736(10)60391-1 [pii]&#xD;10.1016/S0140-6736(10)60391-1 [doi]</electronic-resource-num><remote-database-provider>Nlm</remote-database-provider><language>eng</language></record></Cite></EndNote>}. We did however observe a modest trend of a reduction in serum BNP with allopurinol. There is some



evidence to suggest that BNP may be related to myocardial ischemia. Goetze et al. had previously demonstrated an increase in BNP expression and rapid release of newly synthesised proBNP as a result of myocardial ischaemia{ ADDIN EN.CITE { ADDIN EN.CITE.DATA }}. BNP levels have also been shown to be related to myocardial ischemia in patients with cardiomyopathy{ ADDIN EN.CITE

<EndNote><Cite><Author>Nakamura</Author><Year>2002</Year><RecNum>4837</RecNum><DisplayText><style face="superscript">14</style></DisplayText><record><rec-number>4837</rec-number><foreign-keys><key app="EN" db-id="sde022erm0xppvetfvyv9pv4azzevtattee9" timestamp="1506343353">4837</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Nakamura, T.</author><author>Sakamoto, K.</author><author>Yamano, T.</author><author>Kikkawa, M.</author><author>Zen, K.</author><author>Hikosaka, T.</author><author>Kubota, T.</author><author>Azuma, A.</author><author>Nishimura, T.</author></authors></contributors><auth-address>Department of Radiology, Kyoto Prefectural University of Medicine, Kyoto, Japan. tomnak@koto.kpu-m.ac.jp</auth-address><titles><title>Increased plasma brain natriuretic peptide level as a guide for silent myocardial ischemia in patients with non-obstructive hypertrophic cardiomyopathy</title><secondary-title>J Am Coll Cardiol</secondary-title></titles><periodical><full-title>J Am Coll Cardiol</full-title></periodical><pages>1657-63</pages><volume>39</volume><number>10</number><keywords><keyword>Adult</keyword><keyword>Aged</keyword><keyword>Atrial Natriuretic Factor/blood</keyword><keyword>Cardiomyopathy, Hypertrophic/blood/diagnosis</keyword><keyword>Exercise Test</keyword><keyword>Female</keyword><keyword>Humans</keyword><keyword>Male</keyword><keyword>Middle Aged</keyword><keyword>Myocardial Ischemia/blood/ diagnosis</keyword><keyword>Natriuretic Peptide, Brain/blood</keyword><keyword>Predictive Value of Tests</keyword><keyword>Reference Values</keyword></keywords><dates><year>2002</year><pub-dates><date>May

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(Linking)</isbn><accession-num>12020494</accession-  
num><urls></urls></record></Cite></EndNote>}. Clearly, further studies are needed to  
further investigate this observation.

## Limitations

The present study is relatively small and is likely to be not adequately powered to definitively assess the efficacy of allopurinol in patients with cardiac syndrome X. As this was a cross-over study, there are potential "carry-over" effects between treatments that might have confounded the { [HYPERLINK "http://en.wikipedia.org/wiki/Estimates"](http://en.wikipedia.org/wiki/Estimates) \o "Estimates" } of the { [HYPERLINK "http://en.wikipedia.org/wiki/Effect\\_size"](http://en.wikipedia.org/wiki/Effect_size) \o "Effect size" }. However, we used a 4 weeks wash out period that has been shown to be sufficient in our previous published cross-over study using high dose allopurinol{ ADDIN EN.CITE

<EndNote><Cite><Author>Noman</Author><Year>2010</Year><RecNum>1056</Rec  
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title></titles><periodical><full-title>Lancet</full-title></periodical><pages>2161-  
7</pages><volume>375</volume><number>9732</number><edition>2010/06/15</editi  
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## Conclusion

In patients with cardiac syndrome X, we showed that high dose allopurinol did not improve exercise capacity, coronary or peripheral endothelial function.

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Conflicts of interests (related to this work)

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Faisel Khan: None

Allan D Struthers: None

Chim C Lang: None

**Table 1: Clinical Characteristics of Patients**

<b>Clinical Characteristics of Patients</b>	
Number of patients:	19
Mean Age ( <i>years</i> ):	59 ± 10
Female:	11 (58%)
Body mass index ( <i>kg/m<sup>2</sup></i> ):	30 ± 5
Blood Pressure ( <i>mmHg</i> ):	142/79
Heart Rate ( <i>beats/min</i> ):	70 ± 10
<b>Past Medical History</b>	
Diabetes:	0 (0%)
Hypertension:	14 (74%)
Hypercholesterolemia:	14 (74%)
Family history of coronary artery disease:	12 (63%)
<b>Medications:</b>	
ACE Inhibitors or ARB* ( <i>lisinopril</i>	2 (11%)

<i>or losartan):</i>	
Nitrate ( <i>isosorbide mononitrate or imdur):</i>	7 (37%)
Statin ( <i>simvastatin, atorvastatin or paravastatin):</i>	11 (58%)
Aspirin:	14 (74%)
Ca channel blockers ( <i>amlodipine or diltiazem or nifedipine):</i>	5 (26%)
Beta blockers ( <i>bisoprolol or atenolol):</i>	6 (32%)

\*ARB = angiotensin receptor blocker

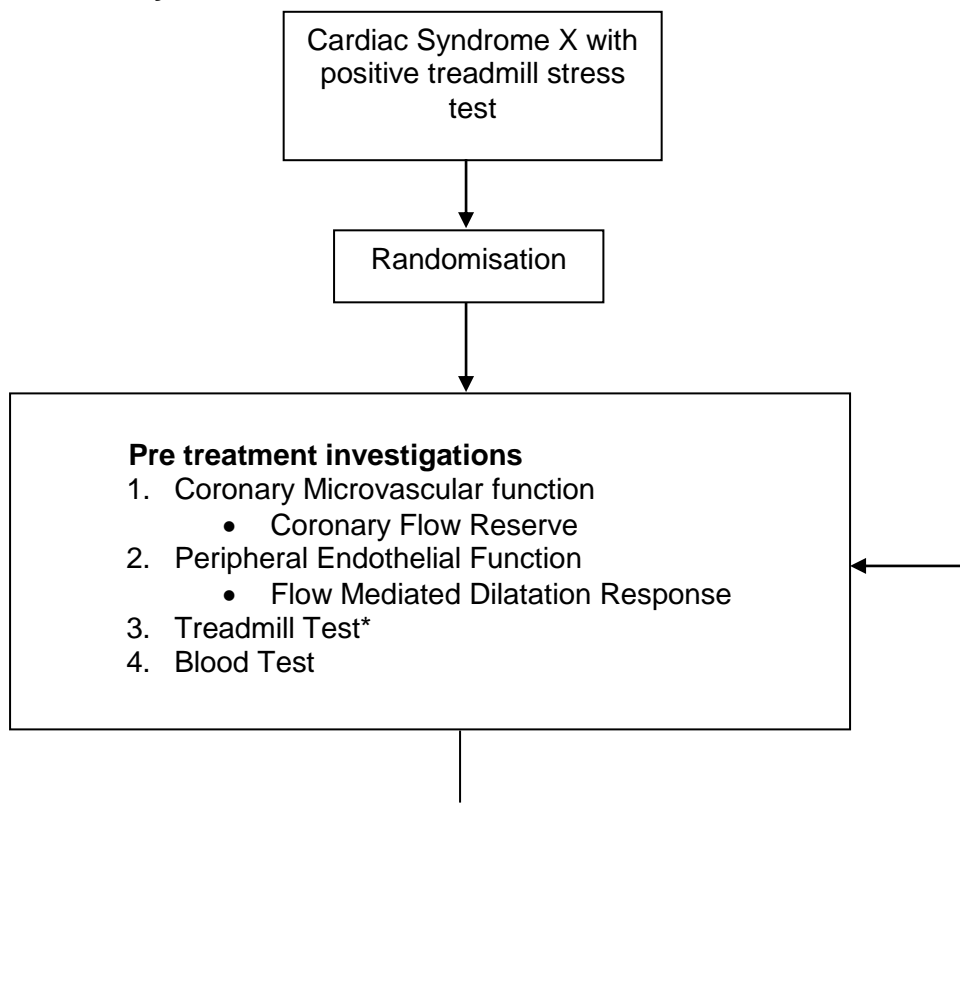
Table 2: Effect of Allopurinol on Serum Uric acid, Endothelial Function and Exercise time.	Allopurinol			Placebo			p-value*
	Pre Treatment	Post Treatment	Absolute Difference	Pre Treatment	Post Treatment	Absolute Difference	
Serum Uric Acid (mmol/L)	0.32±0.08	0.17 ±0.08	-0.16 ±0.09	0.32 ±0.07	0.33±0.07	0.01 ±0.03	<0.001
Serum BNP Level (pg/ml)	6.47 (3.84 to 11.2)	6.28 (3.39 to 15.54)	-8.1% (-22 to 65%)	6.46 (4.55 to 12.5)	9.53 (4.04 to 13.4)	44.4% (-18 to 140%)	0.07**
Coronary Flow Reserve (ratio)	3.63 ±1.04	3.66 ±0.82	0.03 ±0.71	3.50 ±0.80	3.62 ±1.03	0.11 ±0.77	ns
Flow Mediated	6.98 ±	7.20 ±	0.22 ±	6.64 ±2.84	7.05	0.41 ±	ns

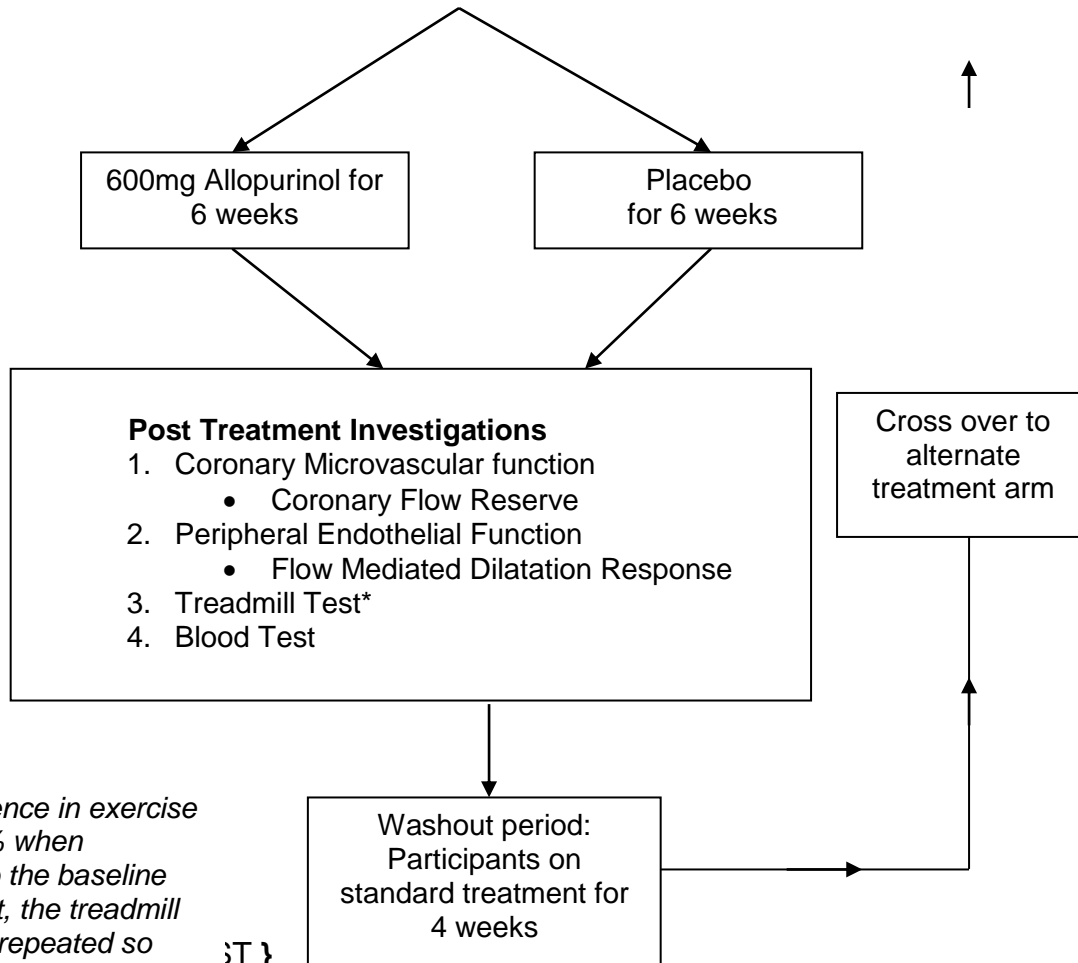
Vasodilatation (%) <i>Endothelium-dependent</i>	2.22	2.58	1.40		±1.62	2.38	
Flow Mediated Vasodilatation (%) <i>Endothelium-independent (GTN)</i>	15.8 ±3.0	16.0 ± 4.5	0.2 ± 2.6	15.5 ± 3.02	16.5 ± 2.5	1.0 ± 1.6	ns
Max. Exercise Time (mins)	8.15 ± 2.43	8.21 ± 1.91	0.06 ± 1.39	8.46 ± 2.15	8.50 ± 2.37	0.03 ± 0.71	ns

\*absolute difference between allopurinol and placebo

\*\* absolute difference expressed as percentage between allopurinol and placebo

**Figure 1: Study Flow Chart**





*\*if the difference in exercise time is  $\pm 15\%$  when compared to the baseline treadmill test, the treadmill test may be repeated so that the highest quality of data can be obtained*

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